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Guest: Dr. Chris Farnsworth is an assistant professor in the Department of Pathology and Immunology at Washington University in St Louis and the medical director of clinical chemistry and point-of-care testing at Barnes Jewish Hospital. Dr. Robert Nerenz is an assistant professor in the department of pathology and laboratory medicine and an assistant director of clinical chemistry at Dartmouth-Hitchcock Medical Center.

Randye Kaye: Hi and welcome to this edition of JALM Talk from the *Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye. Preterm birth, defined as the delivery of an infant prior to 37 weeks gestation places infants at significant risk of death or serious disability. Despite multiple national efforts aimed at reducing premature birth rates, the premature birth rate in the United States has increased in recent years. It remains difficult to identify which women are at risk of preterm birth and who might benefit from therapeutic intervention. Thus, there's considerable interest in the use of biomarkers for this purpose. The May 2021 issue of JALM includes a guidance document written in partnership with the AACC Academy that focuses on laboratory testing for the assessment of preterm delivery. The guidance document describes the currently available biomarkers for preterm birth summarizes the literature evaluating their diagnostic performance characteristics, and provides recommendations for their use in clinical practice. On today's podcast, we're joined by two authors of this guidance document, Dr. Chris Farnsworth is the first author. He's an assistant professor in the Department of Pathology and Immunology at Washington University in St Louis and the medical director of clinical chemistry and point of care testing at Barnes Jewish Hospital.

Dr. Robert Nerenz chaired the guidance document committee and is the senior author. He's an assistant professor in the department of pathology and laboratory medicine and an assistant director of clinical chemistry at Dartmouth-Hitchcock Medical Center. Welcome Dr. Farnsworth and Dr. Nerenz. Can you start by telling us why the AACC Academy sought to put together this guidance document? What are the consequences of preterm birth? And why is it an area of intense research focus?

Robert Nerenz: Yeah. So I think the question about why we put together the guidance document in the first place, there's a fair amount of uncertainty within the lab community about how useful these biomarkers are in the prediction of preterm birth. There are

a number of other guidelines from other professional societies like the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and others, but we really wanted to put something together that was written from more of a lab perspective. As for the consequences of preterm birth, the big one is that prematurity really is the second most common cause of infant death behind birth defects. And for those infants that survive, it's also a cause of significant perinatal morbidity. We have these immediate complications like low birth weight, respiratory distress, long term complications like cognitive impairment, visual and hearing limitations, behavioral and emotional difficulties later in life.

So, for all these reasons, it's something that we really want to get a handle on and reduce the incidence of if we can just from a health outcomes perspective but then also from a financial perspective, it's estimated about $26 billion per year. And so not only do we have the health outcomes but then also the financial piece. And it's a continuing area of research because -- like I said, we haven't really gotten a good handle on this. The preterm birth rate was 9.6% in 2014 that went up to 9.9% in 2017 and then up to 10% in 2018. So, if anything the rate of preterm birth is increasing rather than going the other way.

Randye Kaye: Why is it so difficult to predict?

Chris Farnsworth: So, that's a great question, and it's really a multifactorial problem. The first reason is that the signs and symptoms of preterm labor are relatively non-specific. For example, common symptoms include change in vaginal discharge, there are back ache, cramps, and contractions. These are all very non-specific symptoms. Even in women with a change in vaginal discharge and uterine contractions, symptoms far more associated with preterm labor, 30% will still have spontaneous resolution of these symptoms and 50% will actually go on to deliver a term. So, the symptoms are non-specific for telling you which patients will imminently deliver. So, as a result of this non-specificity, the percent of symptomatic women that will go on to deliver within seven days is consistently less than 5% which by all means the relatively low prevalence outcome. And this again, even in women with symptoms.

So, to put this differently, in the absence of a biomarker, the pretest probability that a woman will not deliver within seven days without performing any lab testing at all is actually 95%. So, it's a really low prevalence outcome. So what's really, truly needed to be helpful for predicting which women with signs and symptoms of preterm labor that will go on to give birth within seven days is a lab test or biomarker that's very

good at ruling in patients that have disease or a test with a very high specificity.

And this is really lab medicine 101 and something we teach pretty frequently to our residents and low prevalence diseases. What's needed most of this test is high specificity, which in turn gives you a greater positive predictive value and will help you rule in preterm birth and as we dive into more of what these biomarkers are, you'll see that a lot of them don't necessarily have the required specificity to fit these needs yet.

Randye Kaye: All right, Thank you. As any woman who has given birth will be test, it doesn't always happen like a dozen in the movies where the water breaks in the middle of the restaurant and you give birth two hours later, preterm or otherwise. So these biomarkers are extremely important as the guidance document focuses on the biomarkers that have been studied so far to evaluate preterm birth. Can you tell us what those biomarkers are and a little bit about them?

Robert Nerenz: So the three that we talk about in detail in the guidance document are fetal fibronectin, interleukin 6, and placental alpha-microglobulin-1 or PAMG-1. So, fetal fibronectin first: it's a protein that's not to mediate implantation and then maintain the placental uterine attachment throughout pregnancy. It's probably the best characterized of the three primary biomarkers we talk about. Lots of literature, lots of different studies and questions and patient populations. But in all those, it's measured in cervical vaginal fluid and increased concentrations in CVF are associated with an increased risk of preterm delivery. As Chris pointed out, it's not super specific and most women who have an elevated fetal fibronectin or a positive fetal fibronectin test result will not go on to deliver within seven days.

So the value of a positive test is limited. The value of a negative test again, because it's a low prevalence condition, you kind of knew before you did the test that the woman was likely not going to deliver in seven days just on the basis of how uncommon of an occurrence this is. To move on then to interleukin 6, it's a cytokine involved in the inflammatory response. So a very different type of protein with a different function. Its concentrations are also increased in cervical vaginal fluid as an indicator of intrauterine inflammation which is also linked in many ways to both preterm birth and then spontaneous term delivery and in terms of performance characteristics, it's pretty similar to fetal fibronectin in terms of positive and negative predictive value.

The last one, PAMG-1, is a protein produced in endometrium during pregnancy. We don't know exactly what it does. It's thought to be involved in potentially a protective response to

oxidative stress. Again, like the other two, concentrations are higher in cervical vaginal fluid in women who deliver prematurely. It does have a better positive predictive value than fetal fibronectin. It's more specific, but still in populations with low prevalence of disease, which is typical of most U.S medical centers, the majority of women who have a positive test for PAMG-1 will still not deliver within seven days. So, even though it's a little bit better than fetal fibronectin and IL 6, it's still not a great test in most patient populations seen at U.S medical centers.

Randye Kaye: All right. Thank you. So not perfect yet. The document talks about that for the most part, professional societies haven't recommended the routine clinical use of these biomarkers for preterm birth and ultimately, the AACC guidance document also does not recommend their routine use. So why is that? Can you summarize for us the limitations of these biomarkers?

Chris Farnsworth: Yeah. So it's actually really interesting but there's disagreement among various professional societies among certain aspects of biomarkers and some have even changed their states overtime. So, for example the American College of Obstetricians and Gynecologists originally stated in 2003 that because of the high negative predictive value of fetal fibronectin it would be useful in ruling out patients that won't go on to have preterm birth. But as Dr. Nerenz just stated, the likelihood of a woman going on to preterm birth with those signs and symptoms is already low. So, a test doesn't actually provide that much value in this context and what's truly needed is the test that's good at ruling in disease or a test with high specificity. So as a result, actually, more recently, I think late in the 2010, 2020 era, the ACOG has updated their stance and no longer actually recommend routine fetal fibronectin testing. In contrast, other societies, such as the Society from Maternal and Fetal Medicine do recommend the occasional use of fetal fibronectin, but only in borderline cases where translational ultrasound length, which is another common tool used for predicting preterm birth, is borderline or not available.

The problem with this approach, there's really a couple, but the biomarkers that we discussed still have potentially the same sensitivity and specificity in these populations. We just don't know because there's not really a lot of good data. In fact, there's no large randomized trials that actually assess the utility of these biomarkers in potentially borderline cases. So, what this has really led to -- has led to people, particularly experts in the field, to propose that we need just better algorithms to assess fetal fibronectin in this context. So clearly more research here is needed, and it may turn out that the biomarkers are useful in this case, but I think it's pretty clear that we just don't know. But as a result, our

guidance document ultimately does not recommend routine used in patients either.

I think just because the data don't support it for routine use. Whether it may provide a little extra value, is impatient their higher risk, or they have a higher pretest probability. So, for example, women who had a previous preterm birth from a previous pregnancy are about two and a half to three times more likely to have a second preterm birth than women who have not previously experienced one. So in this population, actually, the negative predictive value could be more helpful than in the general population. But I think another important distinction that we haven't talked about yet: we've mostly focused on symptomatic women, but there's no societies recommend the use of biomarker testing to adjudicate the risk of preterm birth or preterm Labor and women that are without symptoms.

In fact, there's a lot of really good data from some very reputable journals with large randomized control trials that show that there's just no benefit in this approach. So by and large, the societies are pretty clear here.

Randye Kaye: All right. Thank you. So finally, if you can kind of sum it up, what do you hope that readers are going to take away from this guidance document?

Robert Nerenz: I think just to emphasize what both of us have said a little bit is really what the currently available biomarkers have going for them is the high negative predictive value. But for a low prevalence condition, that really doesn't help us that much and that's kind of the main point that we want people to recognize. The other key point is that anytime you're making a decision about whether a particular test is useful for a particular patient population to really discuss that with clinical colleagues, this isn't a decision that laboratorians should make unilaterally. But really, we need to sit down with our clinical colleagues in OB, particularly, and talk about what is the prevalence of preterm birth in our own institutional patient population. What types of questions are we trying to answer by using these biomarkers and collectively determine what is our institutional approach to testing going to be? Is this something that we believe in or not? Right? And even though the currently available biomarkers have their limitations, preterm birth is still a problem. It doesn't mean that it's just going to go away because we don't have good ways to identify it. And really, what we need is a biomarker with high positive predictive value to take this pool of women with kind of non-specific signs and symptoms, and be able to select the small number of them who will go on to deliver prematurely and then direct our resources appropriately to prolong delivery where clinically appropriate. And then the last piece is kind of taking a step back beyond preterm birth

and just thinking about lab testing in general, is to encourage laboratorians to periodically critically evaluate their test menu and say, do all of the tests that we're performing did actually provide a clinical benefit? Does it make sense for us to continue offering this test? Or are there some that the evidence just isn't there and we need to talk with the clinical stakeholders and decide that maybe it makes sense to stop doing this.

Randye Kaye: All right. Thank you. Those are indeed valuable takeaways and thank you for joining us today.

Chris Farnsworth: Absolutely. Thank you so much for having us.

Randye Kaye: That was Dr. Chris Farnsworth and Robert Nerenz discussing the JALM Special Report "AACC Guidance Document on Laboratory Testing for the Assessment of Preterm Delivery." Thanks for tuning into this episode of JALM Talk. See you next time and don't forget to submit something for us to talk about.